

Safety of low dose heparin in elective coronary angioplasty

Karel T Koch, Jan J Piek, Robbert J de Winter, George K David, Karla Mulder, Jan G P Tijssen, Kong I Lie

Abstract

Objectives—To evaluate the safety of a low dose of heparin in consecutive stable patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA).

Design—Open prospective study in a single centre.

Patients—1375 consecutive patients had elective PTCA (1952 lesions: type A 11%, B1 34%, B2 36%, and C 19%). There were no angiographic exclusion criteria.

Interventions—A bolus of 5000 IU heparin was used as the standard anticoagulation regimen during PTCA. The sheaths were removed immediately after successful completion of the procedure. Prolongation of heparin treatment was left to the operator's discretion.

Main outcome measures—Procedural success was defined as < 50% residual stenosis without death from any cause, acute myocardial infarction, urgent coronary bypass surgery, or repeat angioplasty within 48 hours for acute recurrent ischaemia; the need for prolonged heparinisation; and the occurrence of puncture site complications.

Results—Procedural success without clinical events was achieved in 90% of patients. Mortality was 0.3%; coronary bypass surgery was performed in 1.7% of the procedures. The rate of myocardial infarction was 3.3%; repeat angioplasty within 48 hours was carried out in 0.7% of patients. A total of 89.1% of the patients were treated according to the protocol. Prolonged treatment with heparin was considered necessary in 123 patients (8.9%). Repeat angioplasty for abrupt closure was performed in two patients shortly after sheath removal and in two during prolonged heparinisation. Puncture site complications occurred in 2.1% of patients (low dose heparin 1.9% and prolonged heparinisation 4.9%).

Conclusion—Elective PTCA can be safely performed using a low dose of heparin, with a negligible risk for subacute closure. Low dose heparin may reduce the incidence of puncture site complications, shorten hospitalisation, and enable outpatient angioplasty.

(Heart 1997;77:517-522)

Keywords: angioplasty; anticoagulants; heparin

Systemic heparinisation is universally employed during percutaneous transluminal coronary angioplasty (PTCA). Most patients are treated with empirically determined doses, ranging from 10 000 IU to 15 000 IU. Monitoring of anticoagulation by the activated clotting time is advocated,¹⁻³ but the recommended level of at least 300 seconds has been largely based on studies performed in patients during coronary bypass surgery.⁴⁻⁶

Ischaemic complications during angioplasty have been associated retrospectively with low levels of anticoagulation, and although an optimum cannot be derived from these studies, some have indicated the necessity of more intensive anticoagulation.^{7,8} In contrast, the incidence of bleeding complications seems to be inversely related to the level of anticoagulation.⁹

At our centre a low dose of heparin (5000 IU) was used routinely in elective PTCA for many years for logistic reasons, as hospital facilities were limited with growing numbers of angioplasty procedures. This dose facilitates immediate sheath removal, which may shorten post-procedural immobilisation and hospitalisation and reduce the risk of serious bleeding. Such a regimen, however, may increase the risk of (sub)acute thrombotic closure of the treated segment.

The aim of the present study was to evaluate prospectively the safety of this regimen (standard dose of heparin 5000 IU) in patients undergoing elective PTCA.

Patients and methods

PATIENTS

The series comprised 1375 consecutive, prospectively studied patients who had elective PTCA at the Academic Medical Centre, Amsterdam between January 1991 and December 1993. Selection for angioplasty was based on > 70% stenosis in one or more coronary arteries or bypass grafts, and an anatomy suitable for PTCA.

Exclusion criteria included planned elective stent implantation, laser angioplasty, intra-aortic balloon pump assistance, angioplasty under general anaesthesia, angioplasty performed for acute myocardial infarction, and unstable angina treated intravenously with nitrates and heparin (table 1). Patients stabilised with oral medical treatment having recent onset or progressive angina, angina at rest, or early post-infarction angina (Braunwald classes I and II unstable angina¹⁰) were not excluded. There were no angiographic exclusion criteria.

Academic Medical Centre, University of Amsterdam, The Netherlands: Department of Cardiology

K T Koch
J J Piek
R J de Winter
G K David
K Mulder
K I Lie

Department of Biostatistics and Clinical Epidemiology
J G P Tijssen

Correspondence to:
Dr K T Koch, Department of Cardiology, Academic Medical Centre B2, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

Accepted for publication 3 March 1997

Table 1 Exclusion criteria

	n	%
All procedures during study period	2099	
Excluded		
Unstable angina (Braunwald III)	487	(23.2)
Acute myocardial infarction	59	(2.8)
Elective stent implantation	46	(2.2)
Excimer laser angioplasty	77	(3.7)
Intra-aortic balloon pump support	14	(0.7)
General anaesthesia	8	(0.4)
Other	33	(1.6)
Included	1375	(65.5)

ANGIOPLASTY PROCEDURE

Elective angioplasty was performed by the femoral approach using 7 and 8 French guiding catheters. Patients were pretreated with 300 mg aspirin taken orally. A standard dose of 5000 IU heparin was given as an intra-arterial bolus after insertion of the arterial sheath. A 12 lead electrocardiogram (ECG) was monitored during the entire procedure. Angioplasty was performed by experienced operators with standard interventional guiding catheters, guidewires, and balloons, with on site surgical stand-by. A low osmolar, ionic contrast agent (Hexabrix; Guerbet Laboratories, France) was used.

Activated clotting times (Hemochron Unit; International Technidyne Corp, Edison, New Jersey, USA) were measured in 50 consecutive patients, before and 15 minutes after administration of heparin, and at 30 minute intervals during the procedure. The operator was unaware of the test results.

The procedure was considered to be complete if the angiographic result remained satisfactory five minutes after inflation of the last balloon. The sheaths were removed immediately after completion of the procedure. Haemostasis was obtained by manual compression. The protocol allowed the use of an additional dose of no more than 2500 IU heparin if a procedure lasted for more than 90 minutes. These patients were considered to be treated according to the low dose regimen if no further heparin treatment was given and the sheaths were removed immediately after the procedure.

Whether to give more heparin during the procedure, or to prolong treatment with heparin and to leave the sheaths in place was left to the discretion of the attending interventional cardiologist. In case of prolonged heparinisation, the target activated partial thromboplastin time was 60–80 seconds. Indications for giving higher procedural doses and prolonged treatment with heparin were carefully recorded. Activity of creatine kinase MB was measured six hours after the procedure and repeated when increased until an enzyme peak was recorded. A 12 lead ECG was obtained before the procedure and before discharge. Procedural complications and complications during a 48 hour follow up period were documented.

STUDY END POINTS

The end points of the study were: (1) procedural success; (2) repeat percutaneous intervention for acute recurrent ischaemia; (3)

intracoronary stent implantation for procedural failure; (4) the need for prolonged heparinisation as determined at the operator's discretion; and (5) puncture site complications. Procedural success was defined as < 50% residual stenosis without death from any cause, acute myocardial infarction, urgent coronary bypass surgery for failure of angioplasty, or repeat angioplasty within 48 hours. Myocardial infarction was defined as an increase in the creatine kinase MB fraction of more than twice the upper limit, with or without the development of new Q waves. Puncture site complications were defined as the presence of a major groin haematoma (palpable mass larger than 5 cm), any late bleeding regardless of whether there was measurable loss in haematocrit or a blood transfusion was necessary, pseudoaneurysm, or arteriovenous fistula.

Results

PATIENT CHARACTERISTICS

The study population consisted of 1375 patients (1952 coronary lesions). The mean (SD) age was 60.8 (10.8) (range 31–88) years. Table 2 summarises the main patient characteristics. Documentation of risk factors was complete in 82% of patients. Single vessel disease was present in 47% of patients and multi-vessel disease in 53%. Angioplasty of one coronary segment was performed in 62% of patients and of two or more segments in 38%. The distribution of lesion types according to the American Heart Association/American College of Cardiology (AHA/ACC) classification was type A 11%, type B1 34%, type B2 36%, and type C 19%.

RESULTS OF ANGIOPLASTY

The overall procedural success rate was 90%. Complete revascularisation was achieved in 52% of patients. Four patients died during hospitalisation (0.3%; 95% confidence interval (CI) 0.0 to –0.6) (including one after emergency bypass surgery and one after intracerebral bleeding subsequent to "bail out" stenting). Coronary bypass surgery within 24 hours was performed in 23 patients

Table 2 Patient characteristics (n = 1375 patients)

Mean (SD) age (range) (years)	60.8 (10.8) 31–88
Male	71%
Previous MI	43%
Previous PTCA	26%
Previous CABG	16%
Risk factors	
Hypercholesterolaemia	33%
Smoking	43%
Diabetes	10%
Hypertension	34%
1952 lesions	
Left anterior descending artery	42%
Right coronary artery	28%
Circumflex artery	21%
Saphenous vein graft	9%
AHA/ACC classification	
Type A	11%
Type B1	34%
Type B2	36%
Type C	19%

CABG, coronary artery bypass grafting; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; AHA/ACC, American Heart Association/American College of Cardiology.

Table 3 Results of heparinisation (*n* = 1375 patients)

	No of patients	(%)
Low dose heparin	1225	(89.1)
Uncomplicated	1216	(88.4)
Emergency re-PTCA	2	(0.1)
Non-Q MI	7	(0.5)
Prolonged heparinisation	123	(8.9)
Uncomplicated	78	(5.7)
Q wave MI	7	(0.5)
Non-Q MI	31	(2.2)
Emergency re-PTCA	2	(0.1)
Re-PTCA after re-angiography	5	(0.4)
Death	4	(0.3)
CABG	23	(1.7)

CABG, coronary artery bypass grafting; MI, myocardial infarction; re-PTCA, repeat percutaneous transluminal coronary angioplasty.

Table 4 Activated coagulation times after 5000 IU heparin (50 patients)

	Mean	SD (seconds)
Before heparin	125	34
15 min	259	51
30 min	240	41
45 min	225	51
60 min	212	60

Table 5 Indications for prolonged heparinisation

	<i>n</i> = 123	% of all
Dissection	30 (24%)	(2.2)
"Bail-out" stenting	18 (15%)	(1.3)
Suboptimal result	16 (13%)	(1.2)
Temporary occlusion	16 (13%)	(1.2)
Occluded side branch	15 (12%)	(1.1)
Presence of thrombus	13 (11%)	(0.9)
Other	15 (12%)	(1.1)

(1.7%; 95% CI 1.0 to -2.7). Myocardial infarction (increase in creatine kinase MB of more than twice the upper limit) was present in 45 patients (3.3%; 95% CI 2.3 to -4.2): Q wave infarction in seven and non-Q wave in 38 patients. An MB isoenzyme value was determined in 95% of patients; total creatine kinase activity in 3%. Enzymatic verification was not performed in the remaining 2% of patients without clinical suspicion of myocardial infarction. An additional measurement was obtained the morning after the procedure in 83% of patients. A full set of creatine kinase values was obtained in 12%. Repeat PTCA within 48 hours was undertaken in nine patients (0.7%; 95% CI 0.2 to -1.1). The procedure was unsuccessful but without complications in 57 patients (4.1%).

HEPARINISATION

Angioplasty was performed with 5000 IU heparin in only 1225 patients (89.1%) (table 3). The sheaths were removed immediately

after the procedure. The patients were discharged the next morning. Table 4 summarises the time course of activated clotting time levels of 50 consecutive study patients after administration of a bolus of 5000 IU heparin.

Prolonged heparin treatment was considered necessary in 123 patients (8.9%). Table 5 summarises the indications for prolonged heparinisation. Heparin treatment was continued in the 123 patients and the sheaths were left in place until the next day. These patients were discharged the following morning unless they had a complicated course. The post-procedural course was without complications in 78 of the 123 patients. This group included a further 38 patients with a creatine kinase MB increase of more than twice the upper limit and seven who underwent repeat angioplasty within 48 hours. This procedure was performed as an emergency for subacute closure in two of 1225 patients treated only with 5000 IU heparin, after removal of the sheath, and in two of 123 patients who received prolonged treatment with heparin. Repeat angioplasty was undertaken in another five patients with prolonged heparinisation, because of unsatisfactory angiograms at planned 24 hour follow up (table 3).

The overall incidence of puncture site complications was 2.1% (1.9% (95% CI 1.1 to -2.6) in patients given low dose heparin and 4.9% (95% CI 4.0 to -8.7) in patients treated with prolonged heparinisation). Of 1225 patients allocated to low dose heparin, haematoma > 5 cm occurred in 14 patients, bleeding in three, and vascular complications in six; in 123 patients treated with prolonged heparinisation, these numbers were three, one, and two, respectively.

Discussion

The findings of the present study show the safety and feasibility of low dose heparin in elective PTCA. These results suggest an alternative to the routine use of 10 000-15 000 IU heparin during intracoronary intervention. This approach may shorten hospitalisation time and reduce vascular complications.

The results of this prospective study in consecutive patients indicate that elective angioplasty can be performed with a negligible risk of subacute closure using 5000 IU heparin. The study comprised patients from 1991 to 1993, because anticoagulative treatment was

Table 6 Results of angioplasty (1990-93): comparison with the present study

Reference	Year	No of patients	Success (%)	Death (%)	MI Q/non-Q	CABG (%)	re-PTCA (%)	Stent (%)
Myler <i>et al</i> ¹¹	1990-91	533	92	0	1.7/-	2.1	—	—
Myler <i>et al</i> ^{13*}	1990	220	85	0	6.6	6.1	—	—
Stammen <i>et al</i> ^{14†}	1992	631	91	0.3	3.6‡	4.7	—	—
PARK ¹⁵	1990-92	330	—	0.3	2.1‡	2.0	2.7	—
CAVEAT (balloon) ¹⁶	1991-92	500	91	0.4	2.0/6.0§	2.0	—	0.4
BENESTENT (balloon) ¹⁷	1991-93	257	91.1	0	0.8/2.3‡	1.6	1.2	5.1
STRESS (balloon) ¹⁸	1991-93	202	89.6	1.5	3.0/5.0‡	4.0	1	6.9
Present study	1991-93	1375	90	0.3	0.5/2.8‡	1.7	0.3	1.3

*Initially stabilised unstable angina: defined as onset one to two weeks before angioplasty.

†Initially stabilised unstable angina: defined as angioplasty after 15 days' hospitalisation.

‡Defined as creatine kinase increase more than twice the upper limit of the normal; §more than three times.

CABG, coronary artery bypass grafting; MI, myocardial infarction; re-PTCA, emergency repeat angioplasty.

temporarily altered in 1994 due to an increase in elective stent implantation. At that time a more aggressive antithrombotic regimen was considered necessary for elective stent implantation. A total of 1225 (89.1%) of the 1375 patients were treated according to the low dose heparin protocol and the sheaths were removed immediately after the procedure. Subacute closure occurred in only two of these patients. Prolonged heparinisation was considered necessary in 123 (8.9%), with an uncomplicated course in 61% of these patients.

Our study population does not differ essentially from historical and from the same time period reported series with regard to main characteristics such as age, gender, the extent of coronary artery disease, history of myocardial infarction or previous revascularisation procedures, and the distribution of AHA/ACC lesion types.¹¹⁻¹² The overall results of angioplasty are in accord with the results and ischaemic complications of recent studies regarding balloon angioplasty in elective patients,¹¹⁻¹⁵ as well as the results of prospective randomised studies in a selected cohort of patients¹⁶⁻¹⁸ (table 6). The heparin dose in these reported series was at least 10 000 IU.

The periprocedural myocardial infarction rate reported in the literature varies from 2.6% to 13.5% depending on definition.¹⁹⁻²⁰ The incidence of myocardial infarction in the present study was 3.3% (CI 2.3 to 4.2); 0.5% were Q wave infarctions. In fact, the incidence of myocardial infarction is within the range reported in other studies (table 6) that used the same criterion of an increase in creatine kinase MB of more than twice the upper limit of normal and higher doses of heparin.¹⁴⁻¹⁵⁻¹⁷⁻¹⁸ This finding suggests that the use of low dose heparin during elective angioplasty does not result in an increase in myocardial infarction as determined enzymatically.

In the present study, almost half of acute coronary bypass operations were performed in the first year, reflecting reluctance to accept the results of early experience with "bail-out" stenting. Bail-out stent placement and emergency repeat angioplasty were 1.3% and 0.3%, respectively; however, only a few studies have explicitly addressed both as individual end points related to ischaemia (table 6). In conjunction, the low dose heparin protocol yields similar procedural results compared to those obtained with standard higher or activated clotting time adjusted doses of heparin.

The results of activated clotting time measurements in 50 consecutive patients indicate that most patients did not reach the suggested "threshold" levels of anticoagulation (300 seconds or more) at the beginning and certainly did not do so throughout or before completion of the procedure. The necessity of monitoring anticoagulation during PTCA has been questioned by observations showing no relation between activated clotting times and the occurrence of ischaemic complications.²¹ Others have associated low procedural activated clotting times with a higher rate of in-hospital complications after angioplasty.⁷⁻⁸⁻²² The retrospective design of these studies, how-

ever, does not allow for differentiation as to whether these complications are due to a low level of anticoagulation, or whether the activated clotting time is low because the patient had a complication. A recent study by Narins *et al*²³ showed a significant inverse relation between the degree of anticoagulation during angioplasty and the risk of abrupt closure. These observations are remarkable considering the relatively high initial activated clotting times (median 350 seconds in patients with complications *v* 380 seconds in controls, Hemochron), compared with values obtained in 50 consecutive patients in our study. One can speculate only on the factors influencing these differences. Out of laboratory closure occurred in 34 of 1290 patients (2.6%) compared with four of 1375 patients (0.3%) in our study. It may be that this low incidence relates to the clinical decision making before departure from the catheterisation laboratory in our study. A "safe threshold" could not be identified by Narins *et al*. At present, the optimal activated clotting time level during PTCA is undefined. The results of the present study show the safety of elective angioplasty under "suboptimal" anticoagulation in most patients.

It is conceivable that only a few ischaemic complications of elective angioplasty are actually related to pure thrombus, and that most are primarily related to plaque disruption and dissection, followed by thrombus, or the presence of occlusive intimal flaps that result immediately after balloon injury. If coronary flow can be restored adequately, additional heparin may favourably influence the occurrence of thrombotic sequelae of dissection. This may explain the low rate of ischaemic complications in our study with an initially low dose of heparin, and additional heparinisation in only selected patients.

Triage for treatment with additional or prolonged intravenous heparinisation was based primarily on immediate post-procedural findings considered to be predictive of subacute or late complications. Prolonged intravenous heparinisation may decrease the incidence of subacute closure.⁸⁻²⁴ Prospective studies have failed to show the functional significance of routine heparin treatment for 12-24 hours, but high risk patients were excluded from these studies.²⁵⁻²⁶ It is difficult to substantiate the additional effect of prolonged heparin treatment in patients (8.9%) selected for further heparinisation in our study. Patients who had an uncomplicated course after prolonged heparinisation may have done as well without this treatment, but prolonged heparinisation could not prevent subacute closure in two patients. However, the benign course of the 1225 patients treated with only 5000 IU heparin suggests that proper selection can be made prospectively based on immediate post-procedural results.

The use of platelet glycoprotein IIb/IIIa receptor antagonists may reduce ischaemic complications of angioplasty especially in high risk patients, but is associated with an increased bleeding risk when combined with

standard anticoagulation.²⁷ A reduction in heparin administration might decrease this risk.²⁸ An initial low dose of heparin during angioplasty may facilitate the selective use of such agents when indicated, without an increased risk of puncture site complications.

The incidence of puncture site complications following PTCA with at least 10 000 IU heparin varies from 3.1% to 18%, depending on the definitions used and the diagnostic protocol.^{17 18 29–32} In the present study, puncture site complications were 1.9% (CI 1.1 to –2.6) in patients who underwent angioplasty with low dose heparin. This complication rate is similar to that reported after angiography without heparinisation.^{33 34} The incidence of puncture site complications in patients treated with prolonged heparinisation was 4.9% (CI 4.0 to –8.7). This is in accordance with studies showing that the level of anticoagulation as well as the time period of intensive anticoagulation are independent predictors of puncture site complications.^{26 30–32} Furthermore, the absence of a dwell time of the sheath after completion of angioplasty may have exerted a beneficial effect on the incidence of puncture site complications in the low dose heparin group. The reported sheath dwell times after angioplasty (using 10 000–15 000 IU heparin) vary from four to 10 hours in uncomplicated procedures.^{25 32–34} In the present study, use of low dose heparin allowed immediate sheath removal in most patients (89.1%) with a low risk of puncture site complications. This alternative approach may reduce hospitalisation.

STUDY LIMITATIONS

The present study did not randomly compare different anticoagulation regimens during angioplasty. This open prospective study primarily yields safety data on the low dose heparin regimen in an elective angioplasty population in a single centre experience. The definite answer regarding the optimal dose of heparin in elective PTCA warrants a randomised multicentre dose finding trial. The results of our study, however, question the need of such a trial as comparable ischaemic complication rates can be anticipated at the expense of an increase in puncture site complications with higher doses of heparin. In fact, the results of a recently published randomised comparison have indicated this outcome in a relatively small cohort of patients.³⁵

Myocardial infarction could not be excluded based on enzyme measurements in 2% of the study patients. The expected incidence of an increase in cardiac enzyme in patients without clinical evidence of myocardial infarction after angioplasty is almost 10%²⁰; this indicates that the absence of enzyme determination in 2% of the patients would increase the incidence of myocardial infarction at most from 3.3% to 3.6%, which would not have changed the results essentially. The 3.2% incidence of myocardial infarction may be an underestimation of the true incidence of the rise in enzyme activities related to our protocol of determining creatine kinase values. A full set of creatine kinase values was

obtained in only 12% of patients; two values were obtained in 83% of patients. Our protocol for enzyme detection, however, did not differ from other studies^{19 20} reporting a comparable incidence of enzyme increase after PTCA.

The present study relates to the use of low-dose heparin in conjunction with ioxaglate, which has anticoagulant properties in contrast to the non-ionic contrast media used in many centres. The safety of a small bolus of heparin in conjunction with ioxaglate may not be transferable to non-ionic contrast media.

We could not correct for individual operator bias to select patients for prolonged heparinisation, although the indication to change the anticoagulation regimen had to be documented carefully.

Activated coagulation times were not systematically measured throughout the study. Awareness of these values might have introduced operator bias to change the anticoagulation regimen, unless all these measurements were handled in a blind fashion.

CLINICAL IMPLICATIONS

Elective PTCA can be performed safely using low dose heparin, with a negligible risk of subacute closure. Patients eligible for prolonged heparinisation can be selected appropriately, based on immediate procedural results. An initial low dose of heparin during angioplasty may facilitate the ad hoc use of platelet glycoprotein IIb/IIIa receptor antagonists in selected patients without an increased risk of puncture site complications.

This approach with low dose heparin may shorten hospitalisation after angioplasty, and may reduce the incidence of vascular and bleeding complications.

Furthermore, it may provide the opportunity to perform angioplasty in an outpatient setting, which is of paramount importance at a time of rapidly increasing numbers of coronary interventions, limited hospital facilities, and financial restrictions on healthcare.

We thank Dr Jan W ten Cate, Centre for Haemostasis, Thrombosis, Atherosclerosis and Inflammation Research, Academic Medical Centre Amsterdam, The Netherlands, for advice and critical review of the manuscript, and the technical and nursing staff of our cardiac catheterisation laboratory for skilled assistance.

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